and troponin T) indicates that mutant cardiomyocytes like cells also exhibited a progressive disorganization of their contractile apparatus. This cellular model describes for the first time a complex morphological pathology caused by the dysfunction of an ion channel. Finally, the study of current proton leak in physiological conditions provides helpful understanding on its pathological impact.

Platform: Molecular Dynamics I

82-Plat
All-Atom Simulation and Coarse-Grained Analysis of the Rigor Actomyosin System
Joseph L. Baker[1], Gregory A. Voth[2].
[1]Department of Chemistry, University of Chicago, Chicago, IL, USA,
[2]Department of Chemistry, Institute for Biophysical Dynamics, James Franck Institute, and Computation Institute, University of Chicago, Chicago, IL, USA.
Interactions of actin filaments with myosin motor proteins are important for a variety of cellular functions. The myosin mechanochemical cycle is a complicated sequence of steps including ATP hydrolysis by myosin, binding and unbinding of myosin with actin, and phosphate release from myosin during the force-producing ''powerstroke.'' No high-resolution crystal structure of actomyosin exists, however low resolution data from cryo-EM has allowed a characterization of the rigor state (ATP free) of actomyosin at an atomic level of detail. Here we present the first simulation study at an all-atom level of detail of the myosin II S1 domain in the rigor state interacting with a fully periodic actin filament. Additionally, we study myosin II in the rigor and post-rigor states in the absence of actin. Through a combination of all-atom level and coarse-grained (CG) analysis, we are able to identify effects of myosin binding on the actin filament, the effects on myosin dynamics of being bound to actin, and differences in the collective motions between simulated myosin states. CG level analysis allows further characterization of the influence of myosin binding on the definitions of domains which exhibit collective motion for the actin monomers in the periodic filament, and the identification of CG domains of myosin which interact strongly with actin domains based on a heterogeneous elastic network model analysis.

83-Plat
The Common Functional Dynamics of Molecular Motor and Switch Proteins
Guido Scarabelli, **Barry J. Grant**.
University of Michigan, Ann Arbor, MI, USA.
Understanding how protein ligand binding can promote distinct conformational states, with different affinities for binding partners, is key to understanding the structural basis of protein efficacy. Here we study eight molecular motor and G-protein families that undergo GTP or ATP associated conformational changes to regulate important cell processes, including signal transduction and intracellular transport. Employing comparative structure analysis, accelerated molecular dynamics and Brownian dynamics simulations we unveil the pervasive similarity of functionally associated dynamical fluctuations. Different families were observed to have variable inactive but common active nucleotide biding site configurations. Activating conformational changes that reconfigure analogous nucleotide binding site residues were also observed in nucleotide free molecular dynamics simulations. This result suggests that this common flexibility is an intrinsic feature of these families. In addition, conformational changes at the nucleotide binding site in all families were observed to accompany the concerted rearrangements of distinct family specific sub-domains. These sub-domains range from 16-202 residues in length and are joined to common core structural elements at topologically equivalent sites. Moreover, structural changes, correlated with those at the nucleotide binding site, were found to alter the geometry, dynamics and electrostatic field properties of these sites. Furthermore, Brownian dynamics simulations reveal that for kinesin, ras, rab, and rho families these electrostatic differences can modulate the kinetics of protein-protein association events. In summary, our accumulated results indicate that similar activating conformational changes link nucleotide binding to distal topologically equivalent sub-domains that in turn play a role in modulating distinct protein-protein interactions. We speculate that this fundamental mechanism operates in all motor and switch proteins. These results have implications for allosteric drug development and future protein engineering efforts on these systems.
Images and animations related to this work can be found at:
http://thegrantlab.org/

84-Plat
Structural Ensembles of Intrinsically Disordered FG-Nucleoporins Depend on Force Field
Sarah Rauscher, Helmut Grubmüller.
Max Planck Institute for Biophysical Chemistry, Göttingen, Germany.
Intrinsically disordered proteins (IDPs) fulfill important biological roles including cell signaling, cell cycle regulation, and rubber-like elasticity. IDPs pose a tremendous challenge both to traditional structural determination methods as well as their theoretical description via molecular dynamics (MD) simulations: it is difficult to obtain sufficient data to determine the ensembles of structurally heterogeneous systems. Furthermore, because established MD force fields have been developed primarily to study folded proteins, it is not clear how accurately these force fields are able to describe disordered states.
Here, we performed microsecond-timescale MD simulations using four recently-developed force fields: Amber ff99SB*-ILDN, Amber ff03w, CHARMM22*, and CHARMM36. We studied a set of FG-nucleoporin peptides with sequences derived from yeast Nsp1p. FG-nucleoporins are IDPs responsible for the high selectivity of the nuclear pore complex (NPC). They form a mesh-like structure in the central region of the NPC that controls the passage of macromolecules into and out of the nucleus. FG-nucleoporins are a prototypic example of the biological role of protein disorder, and beyond their particular function are key model systems for disordered proteins.
Overall trends, such as temperature-induced unfolding and differences in compactness between cohesive and extended coil domains of Nsp1p, are described reasonably well by all force fields. However, we find marked differences in the extent of hydrogen bonding and secondary structure preferences. The average chain dimensions with the CHARMM force fields are more than 20% larger than the Amber force fields. Taken together, our results strongly suggest that disordered states are particularly sensitive to force field choice. As a next step, we will therefore compare to experimental measurements of both chain dimensions and secondary structure to determine which force field provides the most accurate description.

85-Plat
Molecular Mechanism of Proflavine Intercalation: Evidence for Drug-Induced Minimum Base-Stacking Penalty Pathway
Arnab Mukherjee.
Indian Institute of Science Education and Research, Pune, India.
DNA intercalation[1] is associated with anti-cancer therapeutics and therefore the process is of enormous interest. Molecular mechanism of DNA intercalation has remained elusive. The previous attempts to understand the molecular mechanism of intercalation[2] indicated that role of DNA structural changes, and origin of multi-step nature[3] of the intercalation process using a de-intercalation pathway. A successful intercalation event, which require transition from several possible out-side bound states to a unique intercalated sate, is not achieved. Here we used an appropriate configurational restraint to witness the process of a direct intercalation mechanism of proflavine. This study answers a long-standing question that intercalation indeed occurs through a drug-induced cavity formation mechanism rather than through natural fluctuation of the DNA[4]. This study shows that in fact intercalation of proflavine proceeds through a minimum base-stacking penalty pathway through minor groove edge of the DNA even though the barrier through major groove is smaller. The reason for such a peculiar observation lies in the more stable minor groove-bound state, which forms fast, however, but depletes slowly due to higher barrier to intercalate. The origin of the higher barrier through minor groove originates from the desolvation energy of the DNA and entropy. The barrier for intercalation through the major groove-bound state, in the absence of desolvation, is entropic in nature. The study also shows, using a simple kinetic scheme that while intercalation happens through minor groove, de-intercalation would likely happen through the major groove having a cyclic intercalation/de-intercalation pathway.[4]
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86-Plat
The Physics of DNA Bending
Aleksander Drozdetski, Alexey Onufriev.
Virginia Tech, Blacksburg, VA, USA.
The majority of DNA in living cells is strongly bent. However, this strong bending regime is poorly understood. While the weak bending regime can be